REMARKS

Claims 1-17, 20, 21 and 23 were pending in the application. Claims 1 to 9, 20 and 21 were examined and rejected, while c1aims 10-17 and 23 had been withdrawn from consideration.

A discussion of the obviousness rejection on the basis of the combination of one newly cited reference and one previously cited reference and Applicants' responses to this single ground of rejection follow.

Applicants thank the Examiner for withdrawal of all the prior claim objections and three rejections under § 102 in response to Applicants' earlier amendments and arguments.

In view of the remarks, below, Applicants believe that the newly made § 103 rejection should be withdrawn and the claims allowed.

I. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-9, 20 and 21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Mavilio, F. *et al., Blood 83*:1988-97, April 1, 1994) (hereinafter **"Mavilio"**) when combined with Setoguchi *et al., J Immunology, 165*:5980-86, 2000 (hereinafter "**Setoguchi**")

A. The Office's Discussion of the References and the Rejection

1. The Primary Reference (**Mavilio**)

Mavilio was cited for teaching collection of human peripheral blood mononuclear cells (PBMCs), culturing the cells for 72 hours with the mitogen PHA and the lymphokine IL-2 to stimulate them. **Mavilio** disclosed viral infection with a LNSN vector[1] containing cDNA encoding human low-affinity nerve growth factor receptor (LNGFR), by exposure of these stimulated human peripheral blood lymphocytes (PBLs) with a cell-free viral stock. PBLs were selected 48 hrs later in medium supplemented with human serum, human recombinant IL-2, and G418. To improve retroviral infection, the PBLs were co-cultivated with virus producing cells for 48-72 hours. The cells were analyzed by flow cytometry for LNGFR expression.

With respect to claim 1, the Office concluded that **Mavilio** teaches modifying at least a portion of mammalian PBMC (which the Offices states include lymphocytes that are not selected or enriched on the basis of antigen specificity. This is because IL-2 stimulation allegedly is non-antigen specific (a point which Applicants believe is not precisely so), introducing an expression construct into these cells, and recovering the modified cells by flow cytometry.

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[1] A retroviral vector constructed by insertion of the LNGFR cDNA into the Hpa I site of the LXSN retroviral vector

Mavilio allegedly meets the limitation of the following claims for the reasons given below:

- Claim 2: because **IL-2** is used to stimulate PBLs, and would thus provide an "enriched" PBL population..
- **C**laim 3: by teaching (transformation of) lymphocytes.
- Claim 4: by teaching culturing the cells for 72 hours prior to viral (vector) infection.
- Claim 5: by teaching use of PHA and IL-2 (which are "proliferating agents")
- Claim 6: by teaching the culture of cells with PHA
- Claim 7: by teaching use of flow cytometry to isolate retrovirus-transduced cells
- Claim 8: by teaching lymphocytes
- Claim 20-21: by teaching production of an enriched lymphocyte population, which includes B lymphocytes, T lymphocytes or CD4+ lymphocytes. Since, claims 20-21 do not specify that the enriched lymphocyte population includes "any specific population of these cells," method allegedly would inherently achieve an enriched population of any combination of these lymphocytes.

Importantly, the Office admits that **Mavilio** differs from the present claims because it does not disclose use of an expression construct that comprises a nucleotide sequence encoding an IL-10 polypeptide.

2. The Secondary Reference (**Setoguchi**)

The above gap or deficiency is allegedly filled by **Setoguchi** which teaches transfection of splenocytes with a retroviral vector encoding IL-10. Accordingly, the Office believes that it would have been obvious to modify the teachings of **Mavilio** to utilize an expression construct that encodes an IL-10 polypeptide, with a reasonable expectation of success. Allegedly, one would have been **motivated** to make this modification by Setoguchi's disclosure of using T cells as vehicles for delivering "useful agents" such as IL-10 -- which is known to mediate immunosuppressive effects predominantly by down-regulating macrophage functions and inhibiting proinflammatory cytokines produced by Th1 cells[2] Thus, **Setoguchi** allegedly established the "importance and efficacy of IL-10 in treatment of inflammatory diseases, including arthritis, and by doing so, suggested the **usefulness of using T cells to deliver therapeutic agents (in this case, IL-10)**. Thus, the Office concluded that the claimed invention, as a whole, is "clearly" *prima facie* obvious in the absence of evidence to the contrary.

[2] and that IL-10 acted to prevent disease expression and development in a collagen-induced arthritis model when administered i.p.as mouse IL-10 protein or as an adenovirus vector encoding murine IL-10

B. Applicants' Response

Applicants believe that had the Examiner carefully considered Applicants' discussion of **Setoguchi** in their last Response (dated Nov. 2, 2006) in view of the reasons for rejection advanced above, she would not have made this rejection in the first place.

Rather than rehash that entire discussion here, Applicants respectfully direct the Examiner's attention to page 8, 4th full para. (*2. Applicants' Response*) to page 10, line 4, of that last Response. Some relevant points will be restated here, nevertheless.

Applicants believe that a more logical path to a rejection based on these two references would have utilized **Setoguchi** as the primary reference and **Mavilio** as the secondary reference. However, irrespective of that, Applicants' position is that his combination, taken in either order, cannot be properly construed as rendering the present claims obvious.

It is important to note ate the outset that the "splenocytes" being transformed with IL-10 in **Setoguchi** are not "merely" murine splenocytes but represent an unusual "engineered" cell population in which the vast majority of T cells are skewed by means of a transgene expressed in the donor mouse to express a single T cell receptor (TCR) which is specific for the antigen ovalbumin (OVA). In other words, the T cells in the donor spleens are a "would-be clone" of T cells, as discussed in **Setoguchi** at page 5982, middle of left col. (under heading *"Transduction of mIL-10..."* (although they are not quite as enriched for a single TCR as is a true clone). The reason for seeking such an unusual source of almost clonal antigen-specific T cells is, as emphasized below, is to have as clean an antigen-specific population as possible, so that it could be activated by stimulation with the specific antigen, OVA (which has nothing to do with the underlying arthritis being treated). Stated otherwise, the only relevant cell population transduced to express IL-10 in **Setoguchi** is a highly selected "antigen-specific" T cell population. Present claim 1, and all the dependent claims, explicitly distinguish this notion by requiring that the IL-10 overexpressing cells

(i) are **not** selected on the basis of specificity for a predetermined antigen and
(ii) treat an inflammatory disease or condition in an **antigen-independent** manner,

and that, when the cells among the PBMCs are lymphocytes, they "are **not selected or enriched on the basis of antigen specificity**..."

This is in stark contrast to **Setoguchi** and was a basis for overcoming the earlier § 102 rejection over **Setoguchi**!

The pending rejection is based on the Office's position that **Mavilio** teaches a "general" method substantially similar to the one claimed - albeit with the important exception that **Mavilio**

provides no suggestion of transforming PBMCs (or any subpopulation of lymphocytes, macrophages, DCs, *etc.*) with a nucleic acid that encodes IL-10. The logic of the rejection is that it would have been obvious to modify **Mavilio** with the **Setoguchi** disclosure by using a retroviral vector encoding IL-10. This appears to be based on the assertion that **Setoguchi** establishes (i) the importance of IL-10 in the treatment of inflammatory diseases and (ii) its suggestion of using T cells to deliver therapeutically relevant agents -- the basis for the alleged motivation to combine the references and for the reasonable expectation of success in doing so.

Applicants submit that this line of reasoning overlooks the most a critical aspect of the **Setoguchi** disclosure, which was noted above. **Setoguchi**'s strategy for treating a murine model of arthritis relies solely on the use of antigen-specific T cells transduced with IL-10. Indeed, **Setoguchi** teaches that achieving this therapeutic effect (amelioration of disease severity) necessarily requires this antigen specificity. At page 5983, left column, first full paragraph (with the heading: *Amelioration of the disease severity requires **Ag-specificity)***, **Setoguchi** describes experiments in which wild-type (*i.e.*, "normal") BALB/c splenocytes transfected with IL-10 (which are not selected nor enriched for specificity for any antigen) were unable to ameliorate the arthritis compared with effectiveness of only the antigen specific "unique" population of transgenic splenocytes; the T cells of this population were almost a clone of antigen- (OVA-) specific cells. The authors concluded:

> "This result indicates that the Ag specificity of the CD4+ T cells is **indispensable** for efficient reduction of disease severity..."

[emphasis added]

Hence **Setoguchi** explicitly teaches away from the present invention as claimed based on its requirements that the IL-10-transduced cells be antigen specific T cells (more particularly, CD4+ T cells) to achieve a useful effect. In contrast to this, the present claims require that cells **not be selected** on the basis of specificity for a predetermined antigen.

Mavilio, the earlier-published of the two cited references, relates simply to a particular method for transfection of peripheral blood lymphocytes and is asserted to provide a protocol for vector-mediated gene transfer and positive selection of the transduced cells. The reference suggests that this protocol may be useful in preparation of modified T lymphocytes.

However, in view of the unequivocal teaching in **Setoguchi** of an absolute requirement for antigen specificity of T cells expressing and presumably delivering IL-10, there appears to be no basis in this combination for a legally sufficient *prima facie* obviousness rejection of the pending claims. If a skilled artisan were to modify the teaching of **Mavilio** according to that of **Setoguchi**, the **Mavilio** method would also need to be modified to start with or to generate an

antigen-specific T cell population (assuming that would have been technically possible other than by the unique transgenic mouse strain selected by **Setoguchi**)). Otherwise, there would be **no** reasonable expectation of success. In fact, if the skilled artisan were to combine the references as envisaged by the Action, there would be every expectation of failure. That is to say, the only way in which a skilled artisan could arrive at the invention **as claimed** by combining the two references relied upon, would be to reject in its entirety the explicit teaching of **Setoguchi**.

In view of the foregoing, Applicants submit that the pending claims are not obvious over **Mavilio** when taken with **Setoguchi** and are thus patentable.

As Applicants suggested above, the Office might have taken a "straighter" path through the same obviousness analysis by beginning with the **Setoguchi** reference (which is more closely related to the instant invention than is **Mavilio**). On that basis, **Setoguchi** would have been the starting point for determining whether or not the claimed invention is obvious and **Mavilio** would have been used for its provision of missing disclosure (about protocols for transducing or transforming the cells. Taking **Setoguchi** as the primary reference, based on Applicants' analysis above, it is insufficient, and the added disclosure of **Mavilio** does not cure that insufficiency. **Mavilio** does not provide material that is missing from **Setoguchi** with respect to the present claims - explicitly, overexpression of IL-10 in a population of cells that is not selected to be antigen-specific. There would have been no motivation for a person skilled in the art to modify **Setoguchi** with **Mavilio** since the person is taught explicitly by the present disclosure and claims not to do so. As stated above, there would be no reasonable expectation of success.[3]

On the basis of the foregoing remarks, Applicants submit that the pending claims are unobvious irrespective of which of the two references relied on by the Examiner is considered to be the "primary" reference. The rejection should therefore be withdrawn.

II. CONCLUSION

In conclusion, it is respectfully requested that the above remarks and requests be considered and entered. Applicant respectfully submits that the present claims are in compliance with 35 U.S.C. § 103 as being nonobvious over the cited art. The claims are therefore in condition for allowance, and Applicants respectfully requests early notice of such favorable action.

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[3] Additionally, there is no basis to reject the present claims as *prima facie* obvious over **Setoguchi** alone due to the critical differences discussed above.

Examiner Thon is respectfully requested to contact the undersigned at the number shown below with any questions or comments if that will assist in understanding this response. Moreover, if only minor amendments or changes are required to put this case into condition for allowance, the undersigned requests that the Examiner call him to discuss the matter before issuing the next paper.

Respectfully submitted,
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